DETAILED ACTION

Application Status

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/31/2008 has been entered.

Applicants' amendment canceled Claims 1-18, 21, and 25-32; amended Claims 19 and 24; and added new Claims 33-37 in the paper of 3/31/2008 is acknowledged. Thus, Claims 19, 20, 22-24 and 33-37 are pending in the instant Office action.

Withdrawn-Objections to the Specification

2. The previous objection of Figure 24 is withdrawn by virtue of Applicants' amendment to the drawings with appropriate corrections.

Objections to the Specification

3. The Sequence Listing filed on 2/4/2004 shows as if the nucleic acid "at" translates into an amino acid Ile (see page 49 in the sequence listing). However, the correct codons for Ile are ATT, ATC or ATA. Appropriate correction is required.

Claim Objections

4. Claims 20, 22, 23, 34-36 are objected to because of the following informalities:

(a) Claims 20 and 34 are identical. Claims 22 and 35 are identical. Claims 23 and 36 are identical. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 19, 20, 22 and 33-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Peter et al. (Journal of Bacteriology, 1996, Volume 178, pages 5229-5234) as evidenced by Pisabarro et al. (1993 May, Journal of Bacteriology, Vol. 175, pp. 2743-2749 as cited in IDS).

Claims 19, 20 and 33-34 are drawn to an isolated polynucleotide molecule comprising a nucleotide sequence encoding the polypeptide consisting essentially of the truncated ORF2 amino acid sequence of SEQ ID NO: 19, wherein said polynucleotide molecule is integrated into the chromosome of a cell of the genus Corynebacterium. Claims 22 and 35 are drawn to a host cell comprising the isolated polynucleotide

molecule of claim 19. The Claims have been interpreted so that the SEQ ID NO: 19 is the truncated ORF2. It is also confirmed by the Applicants' statement "As stated in the specification, SEQ ID NO: 19 is a truncated ORF2" (see page 7, line18, in the Remarks filed on 3/31/2008).

Peter et al. teach that "Genomic DNA was isolated from *C. glutamicum*" (see top right column, page 5229), wherein the genomic DNA comprises the polynucleotide molecule SEQ ID NO: 18; and the isolated DNA in the genome of Peter et al. encodes the polypeptide consisting essentially of the truncated ORF2 amino acid sequence of SEQ ID NO: 19 (or consisting essentially of the SEQ ID NO: 19) as evidenced by the polypeptide and polynucleotide sequence by Pisabarro et al. who teaches the said polynucleotide and encoded polypeptide which is identical to claimed polynucleotide (see the Sequence Alignment in the Attachment). The genomic DNA by Peter et al. meets the limitation of an isolated polynucleotide molecule comprising a nucleotide sequence encoding the polypeptide consisting essentially of the truncated ORF2 amino acid sequence of SEQ ID NO: 19, wherein said polynucleotide molecule is integrated into the chromosome of a cell of the genus Corynebacterium. Thus, the isolated DNA of Peter et al. meets the limitation of Claims 19, 20, 33 and 34. Peter et al. also teach a *C. glutamicum* having the polynucleotide of SEQ ID NO: 18 in a chromosome of the cell, wherein the C. glutamicum meets the limitation of "a host cell" in Claims 22 and 35.

Maintained-Claim Rejections - 35 USC § 103

6. Claims 19-20, 22, 24, 33-35, and 37are rejected under 35 U.S.C. 103(a) as being unpatentable over Pisabarro et al. (1993 May, Journal of Bacteriology, Vol. 175, pp. 2743-2749 as cited in IDS) in view of Labarre et al (1993, Journal of Bacteriology, Vol. 175, p. 1001-1007, as cited previous office actions) and Hirano et al. (US Pat. 6,090,597, Jul 18, 2000, as cited in previous office actions) is maintained.

The rejection was stated in the previous office action as it applied to previous Claims 19-20, 22, and 24. In response to this rejection, applicants have canceled Claims 1-18, 21, and 25-32; amended Claims 19 and 24; and added new Claims 33-37 and traverse the rejection as it applies to the newly amended claims. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

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Applicants argue "Pisabarro does not state that ORF2 is likely translated in lysine biosynthesis. Pisabarro merely states that it is likely that ORF2 is translated". Thus, instant rejection have no prima facie case of obviousness exists. Applicants also argue that if ORF2 of Pisabarro et al. were involved in the Lys synthesis, the Figure 1 would be the ideal place to discuss it.

As applicants acknowledged above, Pisabarro et al. stated that "it is likely that ORF2 is translated in corynebacteria" which is immediately followed by ";studies are in progress to establish whether ORF2 plays a role in lysine biosynthesis" (emphasis

added, see bottom left column, last paragraph, p. 2748). Thus, the use of quotation in the previous office actions by the Examiner is not out of context, as alleged by Applicants. It is up to the author(s) to make decision whether to put any information into the figure or not. It is clear one skilled in the art that Pisabarro et al. is "in progress to establish whether ORF2 plays a role in lysine biosynthesis" based on their study of a locus in the genomic structure; and the instant rejection involves no hindsight(s) nor the assumption(s).

Applicants also argue that "Pisabarro purports to show a complete ORF2. One skilled in the art would recognize that, by definition, a truncated protein is not and cannot be the complete protein". Applicants further argue that "There is nothing to lead one of skill in the art that a truncated ORF2 would have the beneficial properties of the claimed invention that is the use of truncated ORF2.

Applicants acknowledge that the previous statement is true if the claim recites said limitations with the term such as "consisting" in place of the terms "comprising" and "consisting essentially of". Therefore, the recited limitations in claims, i.e., "the polypeptide consisting essentially of the truncated ORF2 amino acid sequence of SEQ ID NO: 19, include the complete protein ORF2 of Pisabarro et al., for example.

Pisabarro et al. teach a gene *orf2* sequence 100% identical to a polynucleotide sequence of SEQ ID NO: 18 and it encodes polypeptide 100% identical to polypeptide sequence of SEQ ID NO: 19 (see SEQ Alignment in the attachment). Pisabarro et al. teach vectors pULAP301 (Figure 2, pp. 2745), pULAP2 (Figure 3, pp. 2748) carrying an orf2 gene and an E. coli host carrying "several constructions carrying dapA, dapB,

ORF2, and combinations of them" (see top left column in pp. 2748). Pisabarro et al. suggest that "it is likely that ORF2 is also translated in corynebacteria" in lysine biosynthesis (see bottom left column, last paragraph on pp. 2748).

Pisabarro et al. do not teach integrating said polynucleotide into the chromosome of a *Corynebacterium*.

Hirano et al. teach successful results to improve "L-lysine Productivity" can be "obtained by the means of amplification of genes for the L-lysine biosynthesis" in a Corynebacterium host cell (see column 1, lines 42-44).

Labarre et al. teach a "reliable and general method" (see Material and Methods" on page 1001-1002 and page 1006, left column bottom) for inserting genes into the chromosome of C. glutamicum. According to Labarre et al., chromosomal integration enhances expression of encoded protein (Table 3) and suggest the technique can be used "in studying and eventually modifying complex host functions such as high-level amino acid production" (see p. 1007, left column, top).

Therefore, It would have been obvious to one of ordinary skill in the art at the time the invention was made to integrate the orf2 gene into the chromosome of C. glutamicum because it is reliable enhancement of expression of a gene. One would have been motivated to integrate the Orf2 nucleic acid of Pisabarro et al. into the chromosome of a C. glutamicum in order to determine if increased expression of Orf2 resulted in increased L-lysine production because of the teachings of Pisabarro et al. (i.e., "it is likely that ORF2 is translated in corynebacteria" which is immediately followed by ";studies are in progress to establish whether ORF2 plays a role in lysine

biosynthesis") and would have used the method of Labarre et al. which is reliable, enhances protein expression and can be used for studying amino acid production as taught by Labarre et al. in the C. glutamicum. One would have had a reasonable expectation of success for inserting the orf2 gene of Pisabarro et al. into the chromosome of a *Corynebacterium* host cell because of the teachings of Pisabarro et al. and Labare et al. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

For the reasons above, the instant rejection is maintained.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652

SEQ Alignment
10/771695

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RESULT 1
THYX_CORGL
ID   THYX_CORGL     STANDARD;      PRT;   250 AA.
AC   P40111;
DT   01-FEB-1995 (Rel. 31, Created)
DT   28-FEB-2003 (Rel. 41, Last sequence update)
DT   10-MAY-2005 (Rel. 47, Last annotation update)
DE   Thymidylate synthase thyX (EC 2.1.1.148) (TS) (TSase).
GN   Name=thyX; OrderedLocusNames=Cg11972, cg2162;
OS   Corynebacterium glutamicum (Brevibacterium flavum).
OC   Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;
OC   Corynebacterineae; Corynebacteriaceae; Corynebacterium.
OX   NCBI_TaxID=1718;
RN   [1]
RP   NUCLEOTIDE SEQUENCE.
RC   STRAIN=ATCC 13869;
RX   MEDLINE=93239702; PubMed=8478336;
RA   Pisabarro A., Malumbres M., Mateos L.M., Oguiza J.A., Martin J.F.;
RT   "A cluster of three genes (dapA, orf2, and dapB) of Brevibacterium
RT   lactofermentum encodes dihydrodipicolinate synthase,
RT   dihydrodipicolinate reductase, and a third polypeptide of unknown
RT   function.";
RL   J. Bacteriol. 175:2743-2749(1993).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RC   STRAIN=ATCC 13032 / DSM 20300 / NCIB 10025;
RA   Nakagawa S.;
RT   "Complete genomic sequence of Corynebacterium glutamicum ATCC 13032.";
RL   Submitted (MAY-2002) to the EMBL/GenBank/DDBJ databases.
RN   [3]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RC   STRAIN=ATCC 13032 / DSM 20300 / NCIB 10025;
RX   PubMed=12948626; DOI=10.1016/S0168-1656(03)00154-8;
RA   Kalinowski J., Bathe B., Bartels D., Bischoff N., Bott M.,
RA   Burkovski A., Dusch N., Eggeling L., Eikmanns B.J., Gaigalat L.,
RA   Goesmann A., Hartmann M., Huthmacher K., Kraemer R., Linke B.,
RA   McHardy A.C., Meyer F., Moeckel B., Pfefferle W., Puehler A.,
RA   Rey D.A., Rueckert C., Rupp O., Sahm H., Wendisch V.F., Wiegraebe I.,
RA   Tauch A.;
RT   "The complete Corynebacterium glutamicum ATCC 13032 genome sequence
RT   and its impact on the production of L-aspartate-derived amino acids
RT   and vitamins.";
RL   J. Biotechnol. 104:5-25(2003).
CC   -!- FUNCTION: Catalyzes the formation of dTMP and tetrahydrofolate
CC       from dUMP and methylenetetrahydrofolate (By similarity).
CC   -!- CATALYTIC ACTIVITY: 5,10-methylenetetrahydrofolate + dUMP +
CC       FADH(2) = dTMP + tetrahydrofolate + FAD.
CC   -!- COFACTOR: Binds 1 FAD per subunit (By similarity).
CC   -!- SUBUNIT: Homotetramer (By similarity).
CC   -!- SIMILARITY: Belongs to the thymidylate synthase thyX family.
CC   ------------------------------------------------------------------------
CC   This Swiss-Prot entry is copyright. It is produced through a collaboration
CC   between  the Swiss Institute of Bioinformatics  and the  EMBL outstation -
CC   the European Bioinformatics Institute.  There are no  restrictions on  its
CC   use as long as its content is in no way modified and this statement is not
CC   removed.
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DR   EMBL; Z21502; CAA79713.1; -; Genomic_DNA.
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DR   InterPro; IPR003669; ThyX_synth.
DR   Pfam; PF02511; ThyX; 1.
DR   TIGRFAMs; TIGR02170; thyX; 1.
KW   Complete proteome; FAD; Flavoprotein; Methyltransferase;
KW   Nucleotide biosynthesis; Transferase.
FT   MOTIF        95    105       ThyX motif.
FT   CONFLICT    214    214       E -> G (in Ref. 1).
SQ   SEQUENCE   250 AA;  28065 MW;  E6C8FF5276BE6314 CRC64;

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Qy        121 LI 122
              ||
Db        121 LI 122

RESULT 13
BLDAPAB
LOCUS       BLDAPAB                 3572 bp    DNA     linear   BCT 18-APR-2005
DEFINITION  B.lactofermentum dapA and dapB genes for dihydrodipicolinate
            synthase and dihydrodipicolinate reductase.
ACCESSION   Z21502 S59668
VERSION     Z21502.1  GI:311767
KEYWORDS    dihydrodipicolinate reductase; dihydrodipicolinate synthase.
SOURCE      Corynebacterium glutamicum
  ORGANISM  Corynebacterium glutamicum
            Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;
            Corynebacterineae; Corynebacteriaceae; Corynebacterium.
REFERENCE   1
  AUTHORS   Pisabarro,A., Malumbres,M., Mateos,L.M., Oguiza,J.A. and
            Martin,J.F.
  TITLE     A cluster of three genes (dapA, orf2, and dapB) of Brevibacterium
            lactofermentum encodes dihydrodipicolinate synthase,
            dihydrodipicolinate reductase, and a third polypeptide of unknown
            function
  JOURNAL   J. Bacteriol. 175 (9), 2743-2749 (1993)
   PUBMED   8478336
REFERENCE   2  (bases 1 to 3572)
  AUTHORS   Martin,J.
  TITLE     Direct Submission
  JOURNAL   Submitted (27-JAN-1993) Martin J., University of Leon, Campus de
            Vegazana s/n, Leon, Spain
COMMENT     On May 3, 2005 this sequence version replaced gi:385798.
FEATURES             Location/Qualifiers
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ORIGIN

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  Matches  365;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

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